

Supplementary Materials

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eTable 1. Search code that was used to identify publications as of March 14, 2023**PubMed search**

#1	covid[Title] OR coronavirus[Title] OR sars-cov-2[Title]
#2	hydroxychloroquine[Title]
#3	randomized[Title/Abstract] OR randomized[Title/Abstract]
#4	#1 AND #2 AND #3

Embase search

#1	covid:ti OR coronavirus:ti OR 'sars cov 2':ti
#2	hydroxychloroquine:ti
#3	randomized:ab,ti OR randomised:ab,ti
#4	#1 AND #2 AND #3

eTable 2. Risk of bias for trials included in the meta-analysis using the Cochrane risk assessment tool. Green circle is for low risk and yellow circle is for some concerns

	Selection bias (Randomization process)	Performance bias (Deviations from the intended interventions)	Attrition bias ¹ (Missing outcome data)	Reporting bias (Measurement of the outcome)	Other sources of bias (Selection of the reported result)
Naggie et al. (HERO-HCQ)					
Abella et al. (PATCH)					
Rajasingham et al. (MN-COVID-PREP)					
Rojas-Serrano et al.					
McKinnon et al. (WHIP)					
Vijayaraghavan et al.					
Polo et al. (EPICOS)					
Llanos-Cuentas et al.					
Grau-Pujol et al.					
Syed et al.					

¹ The Rojas-Serrano et al. study reported minimal loss to follow-up (<10%). The Rojas-Serrano et al. study reported 18% (25/130) lost to follow-up and additional 12% (16/130) discontinued the intervention.

eTable 3. Characteristics of trials included in the meta-analysis

	Naggie et al. (HERO-HCQ)	Abella et al. (PATCH)	Rajasingham et al. (MN-COVID-PREP)	Rojas-Serrano et al.	McKinnon et al. (WHIP)
N (randomization)	1360	132	1496	130	624
Study start date ¹	4/22/2020	4/9/2020	4/6/2020	4/21/2020	4/10/2020
Study completion date ²	1/9/2021	11/13/2020	7/13/2020	3/31/2021	12/14/2020
Occupation	HCWs at risk of COVID exposure through work in the ICU, emergency department, emergency services, respiratory services or COVID unit	HCWs (Physicians, nurses, certified nursing assistants, emergency technicians, respiratory therapists) eligible working >20 hrs/week	HCWs (physicians, nurses, emergency medical technicians) with direct contact with COVID patients including emergency department and ICU setting, first responders and performing aerosol generating procedures	HCWs (nurses, nursing aids, cleaning staff, orderlies, respiratory therapists and physicians) taking care of hospitalized patients with COVID	HCW, first responders and correlational/law officers, nursing home workers, medical students, public transit workers, household family members of HCW in Michigan and Ohio
Sites	34 sites across the US	2 tertiary urban hospitals	Multiple sites nationwide across US and Canada	Single site (National Institute of Respiratory Diseases of Mexico)	Multiple sites at Michigan in the US
Randomization	Yes (Phase III)	Yes (Phase II)	Yes (Phase III)	Yes (Phase III)	Yes (Phase III)
Trial type	Double-blinded	Double-blinded	Double-blinded	Double-blinded	Double-blinded
Eligibility criteria					
Age	>18	>18	>18	>18	>18
Sex	All	All	All	All	All
Weight	No weight requirement	No weight requirement	<40kg excluded	<50kg excluded	N/A
Health conditions					
Allergy or hypersensitivity to HCQ	Excluded	Excluded	Excluded	Excluded	Excluded
G6PD deficiency	Included	Excluded	Excluded	Excluded	Exclude
H/o retinal disease	Excluded	Excluded	Excluded	Included	Exclude
History of significant cardiac disease or Qtc prolongation	Excluded	Excluded	Excluded	Included	
Significant renal disease (stage IV or greater)	Excluded	Included	Excluded	Excluded	Exclude
Pregnant/breastfeeding	Included	Excluded	Included in US, Excluded in Canada	Excluded	Exclude
Medication					
Qtc prolonging medications	Excluded	Excluded	Excluded	Included	Exclude
Use of other medications with significant drug interactions	Included	Excluded	Excluded	Included	N/A
HCQ or other COVID treatments	Excluded (hydroxychloroquine, chloroquine or azithromycin)	Any treatment for COVID-19 within 14 days excluded	Current use of HCQ or chloroquine excluded	HCQ or chloroquine within 30 days excluded	Chronic use of HCQ included
COVID-19 related criteria					
Active or prior COVID	Excluded	N/A	Excluded	Excluded	Excluded
Fevers, cough, SOB	Excluded	Excluded if symptoms within 2 weeks unless negative COVID test	Excluded	Excluded	Excluded
Positive COVID PCR	Excluded	Excluded	Excluded	Excluded	N/A
Positive COVID serology	Included	Included	N/A	Included	N/A
Analysis	Modified intention-to-treat	Intention-to-treat	Intention-to-treat	Intention-to-treat	Intention-to-treat

	Vijayaraghavan et al.	Polo et al. (EPICOS)	Llanos-Cuentas et al.	Grau-Pujol et al.	Syed et al.
N (randomization)	416	454	68	269	200
Study start date ¹	6/29/2020	4/2020 Spain, 10/2020 Bolivia, 3/2021 Venezuela	June, 2020	4/4/2020	5/1/2020
Study completion date ²	2/4/2021	5/30/2021	November, 2020	Study halted a 1 month analysis	Not reported
Occupation	HCWs in an environment with exposure to COVID-19 (physicians, nurses, allied health workers and ancillary health workers)	HCWs (physicians, nurses, medical students, other workers with and without direct patient contact)	HCWs (physicians, nursing staff, technical staff and nursing assistants involved in care of COVID-19 patients)	HCWs (physicians, nurses, nurse assistants and administrators working at least 3 days a week in the trial hospitals)	HCWs at risk of COVID-19 exposure including physicians, nurses, first responders, those performing aerosol generating procedures or working in the emergency department, ICU, and general medicine wards
Sites	9 hospitals across India	Multiple sites across Spain, Venezuela and Bolivia	4 public hospitals across the Lima metropolitan area	3 hospitals in Barcelona, Spain	Single hospital in Pakistan
Randomization	Yes	Yes	Yes (Phase III)	Yes	Yes (Phase II)
Trial type	Unblinded	Double-blinded	Double-blinded	Double-blinded	Double-blinded
Eligibility criteria					
Age	>18	>18-70	>18	>18	>18
Sex	All	All	All	All	All
Weight	No weight requirement	<40kg excluded	No weight requirement	No weight requirement	<40 kg
Health conditions					
Allergy or hypersensitivity to HCQ	Excluded	Excluded	Excluded	Excluded	Excluded
G6PD deficiency	Included	Included	Excluded	Included	Exclude
H/o retinal disease	Excluded	Excluded	Excluded	Excluded	Excluded
History of significant cardiac disease or Qtc prolongation	Excluded	Excluded	Excluded	Excluded	Excluded
Significant renal disease (stage IV or greater)	Included	Excluded	Excluded	Excluded	Excluded
Pregnant/breastfeeding	Excluded	Excluded	Included	Excluded	Excluded
Medication					
Qtc prolonging medications	Excluded	Excluded	Included	Excluded	Excluded
Use of other medications with significant drug interactions	Excluded	Included	Included	Excluded	Excluded
HCQ or other COVID treatments	Excluded (hydroxychloroquine, chloroquine azithromycin)	Any medication as prophylaxis against COVID-19 after 3/1/21	Use of hydroxychloroquine, chloroquine or azithromycin in the last 30 days excluded	Treatment with chloroquine or hydroxychloroquine within the last 1 month	Those already taking hydroxychloroquine were excluded
COVID-19 related criteria					
Active or prior COVID	Excluded	Excluded	Excluded	Excluded	Excluded
Fevers, cough, SOB	Not specified in exclusion criteria	Excluded	Not specified in exclusion criteria	Not specified in exclusion criteria	Excluded
Positive COVID PCR	Excluded	Excluded	Excluded	Excluded	Excluded
Positive COVID serology	N/A	N/A	N/A	Excluded	Excluded
Analysis	Intention-to-treat	Not reported	Intention-to-treat	Intention-to-treat	Not reported

HCW=Healthcare workers; ICU=Intensive care unit; ¹ Date when first participant was enrolled; ² Date when final data were collected for the last participant

eTable 4. Definition of adverse events

Trial	AE definition
Naggie et al. (HERO-HCQ)	Adverse events include general disorders and administration site conditions, psychiatric disorders, skin and subcutaneous tissue disorders, cardiac disorders, infections and infestations, nervous system disorders, gastrointestinal disorders, investigations (electrocardiogram QT prolonged and heart rate increased), ear and labyrinth disorders, renal and urinary disorders, and respiratory, thoracic and mediastinal disorders.
Abella et al. (PATCH)	Adverse events include abdominal pain, anorexia, chest pain, constipation, diarrhea, dizziness, fatigue, gastroesophageal reflux, headache, nausea, paresthesia, rash, and throat tightness.
Rajasingham et al. (MN-COVID-PREP)	Side effects include stomach, diarrhea, neurologic, headache, skin, palpitation, sleep disturbance, tinnitus, vision, allergic reaction, myalgia, bloody nose, appetite change, joint pain, low energy, mouth ulcers, yeast infection, dry mouth, and others.
Rojas-Serrano et al.	Examples of adverse events are as follows: abdominal pain, anorexia, chest pain, constipation, diarrhea, dizziness, fatigue, gastroesophageal reflux, headache, nausea, paresthesia, rash, and throat tightness. Side effects include stomach, diarrhea, neurologic, headache, skin, palpitation, sleep disturbance, tinnitus, vision, allergic reaction, myalgia, bloody nose, appetite change, joint pain, low energy, mouth ulcers, yeast infection, dry mouth, and other.
McKinnon et al. (WHIP)	Covid-19 related symptoms, covid-19 clinical disease and medication adverse effects including gastrointestinal disorders, nervous system disorders, respiratory, thoracic and mediastinal disorders, general disorders and administration site conditions, cardiac disorders, musculoskeletal and connective tissue disorders, psychiatric disorders, skin and subcutaneous tissue disorders, ear and labyrinth disorders, and eye disorders.
Vijayaraghavan et al.	Adverse events listed in each category at the participant level were categorized as cardiac, gastro-intestinal, headache, and Qtc prolongation.
Polo et al. (EPICOS)	Adverse events were classified by organ system and included: gastrointestinal disorders, blood and lymphatic system disorders, cardiac disorders, ear and labyrinth disorders, eye disorder, general disorders, immune system disorder, infections, injuries, investigations, metabolism and nutrition disorders, musculoskeletal/connective tissue disorders, nervous system disorders, psychiatric disorders, renal and urinary disorders, reproductive system disorders, respiratory disorders, skin disorders and vascular disorders.
Llanos-Cuentas et al.	Adverse events from grade 1 to grade 3 and above. Note that the Llanos-Cuentas et al. study did report the number of adverse events (not participants) in the HCQ group only. Due to limited information, it was excluded from the meta-analysis with the adverse event outcome.
Grau-Pujol et al.	Adverse events included: general symptoms (fever, chills, sweating, malaise, myalgia, arthralgia), gastrointestinal symptoms (nausea, abdominal pain, diarrhea, dysgeusia), dermatological symptoms (itching, rash), respiratory symptoms (rhinorrhea, sore throat / odynophagia, cough, pleuritic pain, dyspnea), neurologic symptoms (headache, visual disturbances), and cardiovascular symptoms. Events were graded mild, moderate and severe.
Syed et al.	Syed et al. report the number of patients in each group who experienced adverse events, but did not report what the events were. Due to limited information, it was excluded from the meta-analysis with the adverse event outcome.

eTable 5. Baseline characteristics with additional variables and detailed information. Sample mean and standard deviation (in parenthesis) are reported for continuous variables, and the number of participants and proportion (in parenthesis) are reported for binary or categorical variables.

		Naggie et al. (HERO-HCQ)		Abella et al. (PATCH)		Rajasingham et al. (MN-COVID-PREP)		Rojas-Serrano et al.		McKinnon et al. (WHIP)	
		HCQ	Placebo	HCQ	Placebo	HCQ ¹	Placebo	HCQ	Placebo	HCQ ¹	Placebo
N (randomization)		683	676	66	66	989	494	62	65	387	191
Age		44.2 (11.9)	43.1 (11.2)	31 (20-66) ³	34 (23-62) ³	41.5 (35, 49) ³	40 (34, 48) ³	31.0 (26.4-39) ⁴	31.9 (27.2-43.7) ⁴	45.7 (11.6); 44.9 (11.4) ²	44.1 (12.7)
Female		442 (64.7%)	446 (66.0%)	54 (82%)	37 (56%)	519 (52.5%)	241 (48.8%)	29 (42.6%)	42 (64.6%)	220 (57%)	114 (60%)
BMI (kg/m ²)		28.3 (6.3)	28.6 (6.7)	26 (19-37) ⁵	26 (20-50) ⁵			26.7 (3.9)	27.2 (4.6)		
Current smoker				0 (0%)	0 (0%)	38 (3.84%)	13 (2.6%)	20 (32.2%) ⁶	23 (35.4%) ⁶		
Race/ Ethnicity	White	624 (91.4%)	610 (90.2%)	55 (83%)	54 (82%)	852 (86.1%)	419 (84.8%)			334 (86%)	161 (84%)
	Asian			7 (11%)	7 (11%)	46 (4.7%)	29 (5.9%)			23 (6%)	15 (8%)
	African American	18 (2.6%)	23 (3.4%)	3 (4%)	1 (2%)	10 (1.0%)	10 (2.0%)			15 (4%)	9 (5%)
	Hispanic	39 (5.7%)	40 (5.9%)	0 (0%)	2 (3%)	40 (4.0%)	18 (3.6%)			11 (3%)	7 (4%)
Comorb idities	Asthma	58 (8.5%)	77 (11.4%)	9 (14%)	14 (21%)	91 (9.2%)	59 (11.9%)				
	Diabetes	20 (2.9%)	35 (5.2%)	1 (2%)	3 (5%)	36 (3.6%)	14 (2.8%)				
	Hypertension	99 (14.5%)	99 (14.6%)	3 (5%)	14 (21%)	145 (14.7%)	60 (12.1%)				
	None			54 (82%)	40 (61%)	646 (65.3%)	336 (68.0%)	53 (85.5%)	58 (89.2%)		
Practice Location	Emergency Department	96 (14.1%)	94 (13.9%)	38 (58%)	36 (55%)	417 (42.2%)	190 (38.5%)			48 (12%)	19 (10%)
	Internal Medicine ward			17 (26%)	18 (27%)	98 (9.9%)	56 (11.3%)			31 (8%)	20 (10%)
	ICU/anesthesia			6 (9%)	6 (9%)						
	Labor and delivery			5 (7%)	6 (9%)						
	Ambulance	66 (9.7%)	63 (9.3%)			73 (7.4%)	45 (9.1%)				
	Congregate care setting					46 (4.7%)	20 (4.0%)				
	ICU	48 (7.0%)	59 (8.7%)			184 (18.6%)	85 (17.2%)			37 (10%)	23 (12%)
	Operating room					103 (10.4%)	75 (15.2%)				
	EMS, Fire and Police									32 (8%)	16 (8%)
	First Responders										
Occupation	Nurse	186/677 (27.5%)	167/668 (25.0%)	46 (70%)	42 (64%)						
	Physician	143/677 (21.1%)	144/668 (21.6%)	11 (17%)	16 (24%)						
	Certified Nurse Assistant			2 (3%)	2 (3%)						
	ED Technician			3 (4%)	1 (2%)						
	Respiratory therapist	15/677 (2.2%)	18/668 (2.7%)	3 (4%)	5 (7%)						
	Nurse or Physician							31 (50%)	33 (50.8%)		
	Emergency Medicine Provider					407 (41.1%)	190 (38.5%)				
	ICU provider					160 (16.2%)	83 (16.8%)				
	Anesthesia/ENT					178 (18.0%)	105 (21.3%)				
	HCW in COVID unit					76 (7.7%)	29 (5.9%)				
	Healthcare worker in congregate care setting					11 (1.1%)	4 (0.8%)				
	First responder					115 (11.6%)	65 (13.2%)				

		Vijayaraghavan et al.		Polo et al. (EPICOS)		Llanos-Cuentas et al.		Grau-Pujol et al.		Syed et al.	
		HCQ	Placebo	HCQ ²	Placebo	HCQ	Placebo	HCQ	Placebo	HCQ ¹	Placebo
N (randomization)		213	203	231	223	36	32	142	127	154	46
Age		32.3 (9.65)	31.8 (8.63)	38 (18-65)	38 (18,65)	39.14 (1.53)	39.28 (1.72)	39.6 (11.2)	40.3 (12.8)	30.25 (NA)	31.9 (9.13)
Female		100 (46.9%)	97 (47.8%)	149 (64.5%)	143 (64.1%)	20 (55.6%)	20 (62.5%)	104 (73.2%)	93 (73.2%)	68 (44.1%)	23 (50%)
BMI (kg/m^2)											
Current smoker		8 (3.8%)	9 (4.4%)					21 (14.9%)	17 (13.8%)	19 (12.3%)	7 (15.2%)
Race/ Ethnicity	White										
	Asian										
	African American										
	Hispanic										
Comorb idities	Asthma	0 (0%)	0 (0%)	20 (8.7%)	9 (4.0%)	3 (8.3%)	4 (12.5%)	5 (3.5%)	2 (1.6%)		
	Diabetes	7 (3.3%)	3 (1.5%)	1 (0.4%)	3 (1.3%)	1 (2.8%)	0 (0%)	0 (0%)	1 (0.8%)	4 (2.6%)	3 (6.5%)
	Hypertension	2 (0.9%)	3 (1.5%)	4 (1.7%)	19 (8.5%)	3 (8.3%)	2 (6.3%)	2 (1.4%)	3 (2.4%)	7 (4.5%)	2 (4.3%)
	None										
Practice Location	Emergency Department	26 (12.2%)	18 (8.9%)	20 (8.7%)	21 (9.4%)						
	Internal Medicine ward	130 (64%)	130 (61%)								
	ICU/anesthesia										
	Labor and delivery										
	Ambulance			0 (0%)	0 (0%)						
	Congregate care setting										
	ICU	53 (24.9%)	53 (26.1%)	17 (7.4%)	13 (5.8%)						
	Operating room										
	EMS, Fire and Police First Responders										
Occupation	Nurse	67 (31.5%)	68 (33.5%)	67 (29.0%)	72 (32.3%)	6 (16.7%)	5 (15.6%)	35 (27.8%)	40 (28.2%)	20 (13.0%)	9 (19.6%)
	Physician	34 (16%)	31 (15.3%)	74 (32%)	66 (29.6%)	23 (63.9%)	16 (50%)	67 (47.2%)	53 (42.1%)	118 (76.6%)	25 (54.3%)
	Certified Nurse Assistant					1 (2.8%)	0 (0%)	12 (8.5%)	12 (9.5%)		
	ED Technician										
	Respiratory therapist										
	Nurse or Physician										
	Emergency Medicine Provider									2 (1.3%)	0 (0%)
	ICU provider										
	Anesthesia/ENT										
	HCW in COVID unit										
	Healthcare worker in congregate care setting										
	First responder									2 (1.3%)	0 (0%)

HCQ=Hydroxychloroquine ; ITT= Intention-to-treat ; BMI=Body mass index ; ICU=Intensive care unit; ED=Emergency department ; ENT=Ear, nose, throat ; HCW=Healthcare worker

¹ More than one HCQ groups with different doses are lumped.

² The Polo et al. study randomized participants to four treatment groups, and the HCQ and control groups are used in our meta-analysis.

³ Median (range)

⁴ Median (IQR)

⁵ Mean (range)

⁶ Current or previous smoker

eTable 6. Results of outcome measures in trials included in the meta-analysis. Sample size and the number of participants who had each outcome are reported with proportions (%) in parentheses.

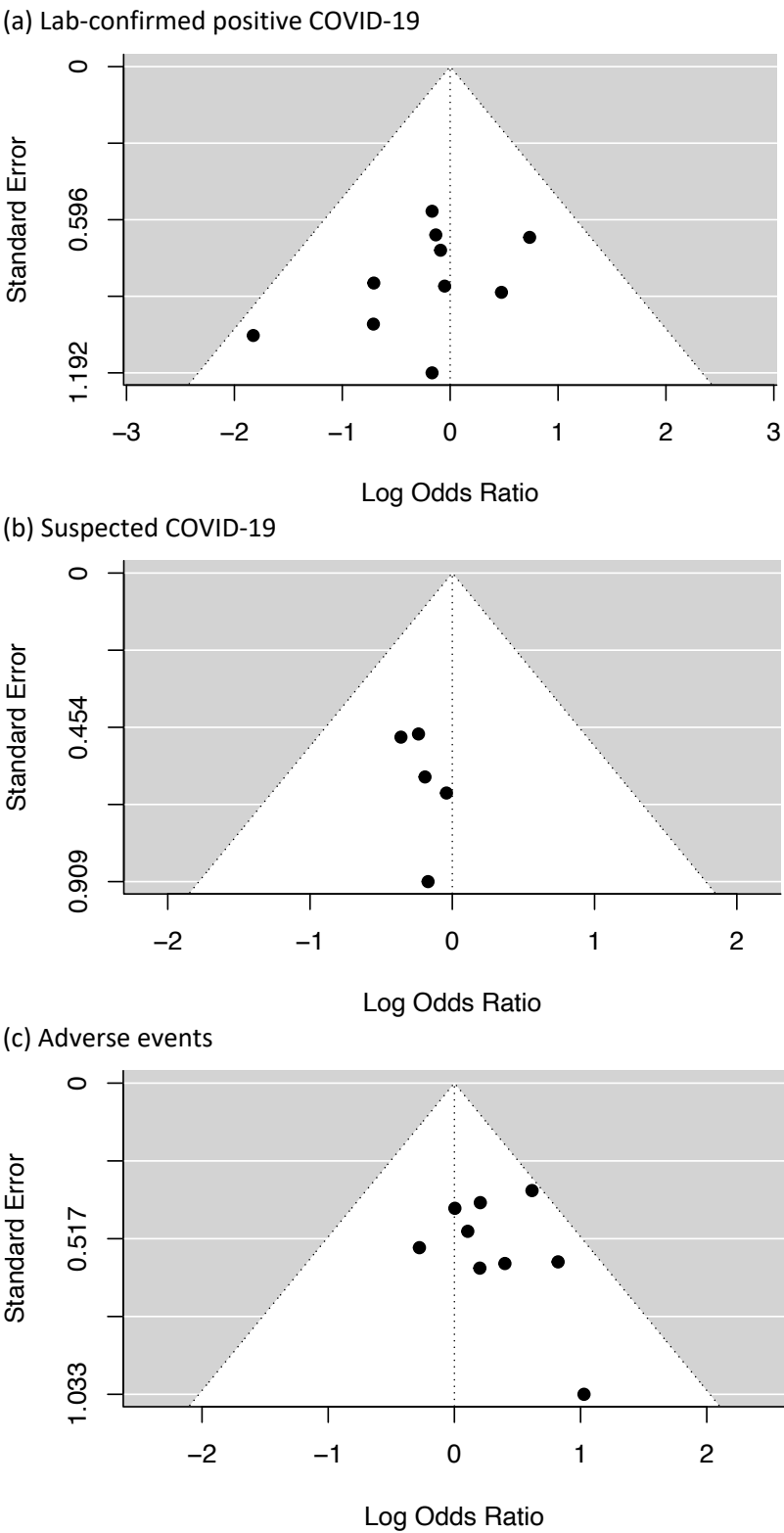
	Treatment	N (ITT)	Confirmed COVID-19	Suspected with COVID compatible symptoms	Adverse event ²
Naggie et al. (HERO-HCQ)	HCQ	683	3 (0.4)	38 (5.6)	16 (2.3)
	Placebo	676	6 (0.9)	47 (7.0)	13 (1.9)
Abella et al. (PATCH)	HCQ	64	4 (6.3)		29 (45.3)
	Placebo	61	4 (6.6)		17 (27.9)
Rajasingham et al. (MN-COVID-PREP)	HCQ ¹	989	11 (1.1)	47 (4.8)	316 (32.0)
	Placebo	494	6 (1.2)	33 (6.7)	100 (20.2)
Rojas-Serrano et al.	HCQ	62	1 (1.6)		32 (51.6)
	Placebo	65	6 (9.2)		38 (58.5)
McKinnon et al. (WHIP)	HCQ ¹	387	2 (0.5)	22 (5.7)	192 (49.6)
	Placebo	191	2 (1.0)	13 (6.8)	85 (44.5)
Vijayaraghavan et al.	HCQ	211	11 (5.2)	12 (5.7)	21 (10.0)
	Placebo	203	12 (5.9)	12 (5.9)	14 (6.9)
Polo et al. (EPICOS)	HCQ	224	21 (9.4)		100 (44.6)
	Placebo	211	23 (10.9)		94 (44.5)
Llanos-Cuentas et al.	HCQ	34	5 (14.7)		
	Placebo	31	3 (9.7)		
Grau-Pujol et al.	HCQ	137	1 (0.7)	3 (2.2)	53 (38.7)
	Placebo	116	1 (0.9)	3 (2.6)	42 (36.2)
Syed et al.	HCQ ¹	154	42 (27.3)		9 (5.8)
	Placebo	46	7 (15.2)		1 (2.2)

HCQ= Hydroxychloroquine; ITT= Intention-to-treat; AE=Adverse event ; COVID-RS=COVID-19 related symptoms ; Vit C= Vitamin C

¹ More than one HCQ groups with different doses are lumped.

² Number of patients with any adverse events

eFigure. Funnel plots for the three outcomes



eTable 7. GRADE summary of findings table

Outcomes	No of participants (studies) Follow up	Quality of the evidence (GRADE)	Odds ratio (95% Confidence Interval)
Lab-confirmed positive COVID-19	5039 (10 studies) From 28 days to 180 days	⊕⊕⊕⊖ Moderate ¹ due to imprecision	0.92 (0.58, 1.37)
Suspected COVID-19	4087 (5 studies) From 56 days to 180 days	⊕⊕⊕⊖ Moderate ¹ due to imprecision	0.78 (0.57, 1.10)
Adverse events	4979 (9 studies) From 56 days to 180 days	⊕⊕⊕⊖ Moderate ² due to imprecision	1.35 (1.03, 1.73)

¹95% confidence interval includes effect suggesting benefit as well as no benefit.

²Although the 95% confidence interval includes an effect suggesting no benefit, we decided to downgrade it by one level because the lower limit is close to the null.

GRADE Working Group grades of evidence is available here:

<https://gdt.gradeapro.org/app/handbook/handbook.html>